

## **REMARKS**

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Applicants have amended claims 1, 3, 14, 30 and 41.

Claim 1 has been amended to include the limitation from claim 2 and this amendment is supported by the original claim 2. As such, no new matter has been introduced.

Claim 3 is amended to correct dependency.

Claim 14 has been amended to correct a typographical error that had omitted representation of R<sub>A</sub> and R<sub>B</sub>. This amendment is supported by the original claim 1. As such, no new matter has been introduced.

Claim 30 has been amended to correct a typographical error in the spelling of the word "patient". The amendment is clerical. No new matter has been introduced.

Claim 41 has been amended to correct a grammatical error. No new matter has been introduced.

These amended claims are supported by the original claims 1, 14, 30 and 41. As such, these amendments do not introduce new matter, and their entry is respectfully requested.

Applicants have cancelled claim 2.

Applicants have added a new dependent claim 46, that is dependent of claim 1. Support for this claim is found in the original claim 1. As such, no new matter has been introduced and its entry is respectfully requested.

## **Responses to the Claim Rejections**

Claim Rejection - 35 USC § 112 second paragraph:

The Examiner alleged that the limitation R<sub>3</sub> is not defined in claim 1 and as such, there is insufficient antecedent basis for claims 4 and 5. Applicants respectfully submit that R<sub>3</sub> is clearly defined in claim 1 – see the 5th line commencing "R<sub>10</sub>, R<sub>11</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>3</sub> each

independently...". Accordingly, there is also proper antecedent for claims 4 and 5. Therefore, the rejections of claims 1, 4 and 5 are obviated.

Claim Rejection - 35 USC § 112 first paragraph:

The Examiner alleged that there is no antecedent basis in claim 14 for hydrogen in all of the definitions of  $R_A$  and  $R_B$ . Applicants have amended claim 14 to correct the typographical error that had omitted representation of  $R_A$  and  $R_B$ . Accordingly, Applicants contends that the rejection of claim 14 is moot.

Claim Rejection - 35 USC § 112 first paragraph:

The Examiner has rejected claims 30-33 for containing subject matters which are not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree and request that the Examiner is kindly reconsider the rejection of claims 30-33. The Examiner's attention is directed to Example 18, which is disclosed from paragraph 0334 of the description and which refers to experiments conducted on rat liver microsomes (sub-cellular organelles) to demonstrate the ability of compounds of the invention to afford strong protection against oxidative stress and resultant free radical-mediated damage. This model has been extensively published in the literature as a means of assessing dietary antioxidants for biopotency, thereby providing information on the key antioxidant components responsible for the health benefits observed in people consuming diets high in these agents. Moreover, these health benefits relate to long term consumption of such diets affording prophylaxis against the emergence of age-related diseases in which chronic oxidative stress is implicated. The experimental protocol described in Example 18 involved adding the compounds to rat liver microsomes 30 minutes prior to the induction of oxidative stress, not at the time of oxidative stress. Consequently, it is strongly contend that the ability of these compounds to effectively protect membranes from a downstream oxidative event constitutes evidence of prophylaxis in a biologically-relevant model. This would be readily apparent to a person skilled in the art.

Claim Rejection - 35 USC § 103(a):

Many naturally occurring flavonoids e.g. myricetin and quercetin are known to have good antioxidant properties as they are easily oxidized, but they do not defend biological membranes well from oxidative damage.

Prior to the present invention, persons skilled in the art believed that antioxidant activity of flavonoid compounds was dependent upon the presence and positioning of OH groups on the A, B and C rings, with particular emphasis on the necessity of the presence of OH groups on both the A and B rings (the A, B and C rings being as show in claim 1 the present application). The importance of having OH groups on the A ring for antioxidant activity is exemplified in "Structure-Antioxidant Activity Relationships Of Flavonoids And Phenolic Acids; Rice-Evans et al.; *Free Radical Biology & Medicine*, Vol. 20, No. 7, pp 933-956, 1996" (copy of Exhibit A attached), see especially page 938, right-hand column, lines 11-23; page 943, bullet point 3; and page 946, left-hand column, lines 23-26.

In the present invention, the inventors found, contrary to their expectations, that the removal of all OH groups from the A ring does not result in loss of antioxidant activity. Further, the inventors also found that when the OH groups on the A ring are substituted with a lipophilic group, RA in claim 1, the compound appears to attach and orientate the flavonoid-like head group on biological membranes so as to defend the biological membrane from oxidative attack.

The surprising properties of the compounds of the present invention are clearly demonstrated in the present application. In this regard, reference is drawn to the comparative examples provided under the heading "Background" (paragraph 0335) and in Figures 2a of the present application. The data in Table 1 and in Figure 2a clearly shows that the compounds of the present invention, though absent any OH groups on the A ring, provide antioxidant activity which is at least as efficacious as myricetin (myricetin being the most potent antioxidant of the known naturally occurring flavonoids – c.f. myricetin is a more potent antioxidant than quercetin (QC), which is disclosed in Miranda and cited in the present Office Action). Whilst myricetin is the most potent antioxidant of the known naturally

occurring flavonoids, it is demonstrated to provide a poor defence against oxidative attack of biological membranes. In contrast, as shown in Table 2 and in Figure 2a, the compounds of the invention (9c-9j) all demonstrate better defence against oxidative attack of biological membranes. A person skilled in the art would have expected the compounds of the present invention to demonstrate less defence against oxidative attack than myricetin because the OH groups had been removed from the A ring, whereas in fact the comparative examples demonstrate improved defence against oxidative attack: this is very surprising.

It should be noted that, in the present invention, the compound of Formula 1 defined in new claim 1 requires at least two hydroxy (OH) groups on the B ring, wherein one of the OH groups is positioned on the C12 (para) position of the B ring and the at least one other OH group may be located at the R<sub>10</sub>, R<sub>11</sub> or R<sub>13</sub> positions. It should be further noted that R<sub>A</sub> and optional R<sub>B</sub> are the only substituents on the A ring.

In contrast, none of Ichimose, Paladini and Miranda discloses a compound which meets the definition of Formula 1 of claim 1. For example:

- i) Ichimose: Compounds disclosed in Ichimose:
  - a) May comprise only one OH group on the B ring. There is no suggestion that this OH group must be in the para position, let alone that two OH groups may be on the B ring, one of which must be in the para position.
  - b) Must comprise an alkyl group R<sup>1</sup> and an OH group on the C3 position of the C ring. There is no suggestion that only one or neither of these substituents may be present.
  - c) May comprise an alkyl group on the A ring. However, there is no suggestion that R<sub>2</sub> must be an alkyl group on the A ring when R<sub>3</sub> is an OH group located at the para position of the B ring.
- ii) Paladini: Compounds disclosed in Paladini:
  - a) May be substituted with one or more NO<sub>2</sub> groups on the B ring. There is no suggestion that any of the NO<sub>2</sub> groups may be substituted for an OH group, let alone that the B ring must have at least two OH groups where one group is in the para position.
  - b) May be substituted on the A ring, but none of the disclosed substituents is a C2-C30 alkyl groups. There is no suggestion that any of R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> or R<sub>11</sub> must be an alkyl

group on the A ring.

- iii) Miranda: Compounds IX, 6PN, 8PN, DPN, 6GN and 8GN on page 3878 of Miranda comprise only one OH group on the B ring. These compounds also include OH groups on the A ring, which groups are absent from the compound of Formula 1 in claim 1.

Further, none of the citations discloses or suggests that removal of all OH groups and addition of a lipophilic chain ( $R_A$ ) on the A ring and use of two OH groups on the B ring would provide compounds which demonstrate improved defence for biological membranes against oxidative attack over equivalent OH containing compounds.

With regard to Ichimose, the compounds of formula (1) are disclosed to accelerate differentiation and proliferation of hair matrix cells. However, there is no teaching or suggestion that any antioxidant properties of the compounds, if any, are improved when at least two OH groups are positioned on the B ring, one of which is at the para position, and the only substituent(s) on the A ring is an alkyl group. Furthermore, Ichimose is entirely silent with regard to compounds which demonstrate improved defence to oxidative attack on biological membranes: Ichimose is solely concerned with hair nourishing and growing effects.

With regard to Paladini, particularly Col 1, lines 25-42, there is no suggestion to replace any of  $R_{1,4}$  with an alkyl group at the same time as making  $R_5$  an OH group in the para position on the B ring as well making a further OH group substitution on the B ring. Paladini is concerned with anxiolytic activity of the compounds and certainly makes no teaching or suggestion of compounds which demonstrate improved defence to oxidative attack on biological membranes.

With regard to Miranda, there is no teaching or suggestion that removal of OH groups and insertion of a lipophilic group ( $R_A$ ) on the A ring would provide compounds which demonstrate improved defence to oxidative attack on biological membranes.

For these reasons the obviousness rejection is improper and should be withdrawn. In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

In the event that there are any questions relating to this Amendment or to the application in general, it is kindly requested that the Examiner contact the undersigned attorney concerning the same to expedite prosecution of this application.

Entry of the foregoing and prompt and favorable consideration of the subject application on the merits are respectfully requested.

Fee deficiencies may be charged and overpayments credited to the NIXON PEABODY LLP Deposit Account No. 50-0850.

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Respectfully submitted,

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